

# OPTION TABLE DECISION AID: FOR A PATIENT WITH RHEUMATOID ARTHRITIS CONSIDERING STARTING THEIR FIRST DMARD

	RECOMMENDED OPTIONS			
Medication options	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide
Year of FDA approval	1955	1996	1988	1998
How taken	Pill	Pill	Pill	Pill
Frequency	Once a day	Twice daily	Once a week	Once a day
Benefits				
Power to suppress arthritis (ACR 20)	43 of 100 will improve	57 of 100 will improve	65 of 100 will improve	60 of 100 will improve
Power to slow joint damage (0-4+)	0	1+	3+	2+
Harms				
Risk of serious infection (hospitalization/100 patient years of use)	0	<1 of 100	2 of 100	3 in 100
Other risks and side effects	Stomach upset, rare eye scarring, rare muscle damage	Sulfa allergy, sunburn, stomach upset, rare liver or lung irritation	Nausea, fatigue, liver scarring, low blood levels, lung scarring	Diarrhea, liver scarring, low blood levels, lung scarring
Special population considerations	Low risk in pregnancy; low blood levels if G6PD deficient	Low risk in pregnancy; can reduce sperm counts	Avoid pregnancy; caution in severe kidney disease; limit alcohol	Avoid pregnancy; limit alcohol
Practical Issues				
Safety monitoring plan (ACR guidelines)	Screen for G6PD if at high risk; eye exam every 12 months	Labs every 1-3 months	Pretreatment: CXR, hepatitis B and C; labs every 1-3 months	Pretreatment: CXR, hepatitis B and C; labs every 1-3 months
What is my monthly cost? (dependent on health plan)				

DMARD=disease modifying anti-rheumatic drug. G6PD=glucose-6-phosphate dehydrogenase deficiency. ACR=American College of Rheumatology. CXR=chest x-ray.

Updated: August 21, 2018 © Richard W. Martin, MD, MA. Free use for clinical care is permitted without license.

# FACTS AND NUMBERS BEHIND THIS DECISION AID

## FDA Medication User Guides

- Hydroxychloroquine: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/009768s041lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/009768s041lbl.pdf)
- Leflunomide: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020905s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020905s020lbl.pdf)
- Methotrexate: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/008085s066lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl.pdf)
- Sulfasalazine: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/007073s124lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/007073s124lbl.pdf)

## Cochrane Database of Systematic Reviews <http://www.cochranelibrary.com/topic/Rheumatology/>

- Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C. [Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic DMARD for rheumatoid arthritis: A network meta-analysis](#). Cochrane Database Syst Rev. 2016 Aug 29;(8): CD010227. Accessed 8/5/2018: <http://dx.doi.org/10.1002/14651858.CD010227.pub2>.
- Osiri M, Shea B, Welch V, et al. [Leflunomide for the treatment of rheumatoid arthritis](#). Cochrane Database Syst Rev. 2002. DOI: 10.1002/14651858.CD002047. Accessed 8/5/2018: <http://dx.doi.org/10.1002/14651858.CD002047>.
- Suarez-Almazor ME, Belseck E, Shea B, Tugwell P, Wells GA. [Sulfasalazine for treating rheumatoid arthritis](#). Cochrane Database Syst Rev. 1998. DOI: 10.1002/14651858.CD000958. Accessed 8/5/2018: <http://dx.doi.org/10.1002/14651858.CD000958>.

## Other Publications

- [Arava \(leflunomide\) \[package insert\]](#). Bridgewater, NJ: Sanofi-aventis U.S LLC; 2016.
- Bathon J, Martin RW, Fleischmann RM, et al. [A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis](#). *N Engl J Med*. 2000;343:1586-1593.
- Caporali R, Caprioli M, Bobbio-Pallavicini F, Montecucco C. [DMARDS and infections in rheumatoid arthritis](#). *Autoimmun Rev*. 2008; 8:139-143.
- Carroll GJ, Thomas R, Phatouros CC, et al. [Incidence, prevalence and possible risk factors for pneumonitis in patients with rheumatoid arthritis receiving methotrexate](#). *J Rheumatol*. 1994;21:51-54.
- Chopra A, Saluja M, Lagu-Joshi V, Sarmukadam S. [Leflunomide \(Arava™\) is a useful DMARD in Indian \(Asian\) patients: a study of 1-year treatment](#). *Clin Rheumatol*. 2008; 27:1039-1044.
- Donahue KE, Gartlehner G, Jonas DE, et al. [Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis](#). *Ann Intern Med*. 2008;148(2):124-134.
- Kalden JR, Schattenkirchner M, Sørensen H, et al. [The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study](#). *Arthritis Rheum*. 2003; 48:1513-1520.
- Katchamart W, Trudeau J, Phumethum V, Bombardier C. [Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis](#). *Cochrane Database Syst Rev*. 2010 Apr 14;(4):CD008495.
- Maddison P, Kiely P, Kirkham B, et al. [Leflunomide in rheumatoid arthritis: recommendations through a process of consensus](#). *Rheumatology (Oxford)*. 2005; 44:280-286.
- O'Dell J, Blakely KW, Mallek JA, et al. [Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine](#). *Arthritis Rheum*. 2001; 44:2235-2241.
- Sawada T, Inokuma S, Sato T, et al; Study Committee for Leflunomide-induced Lung Injury, Japan College of Rheumatology. [Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis](#). *Rheumatology (Oxford)*. 2009; 48(9): 1069-1072.
- Sharp JT, Strand V, Leung H, Hurley F, Loew-Friedrich I. [Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis](#). Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum*. 2000; 43:495-505.
- Singh JA, Saag KG, Bridges SL Jr, et al; American College of Rheumatology. [2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis](#). *Arthritis Care Res (Hoboken)*. 2016 ;68(1): 1-25.
- Smolen JS, Kalden JR, Scott DL, et al. [Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial](#). European Leflunomide Study Group. *Lancet*. 1999; 353:259-266.
- Walker AM, Funch D, Dreyer NA, et al. [Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis](#). *Arthritis Rheum*. 1993;36:329-335.

# OPTION TABLE DECISION AID: FOR A PATIENT WITH RHEUMATOID ARTHRITIS CONSIDERING STARTING THEIR SECOND DMARD

	RECOMMENDED OPTIONS			
Medication options	Triple Therapy (HCQ+SSA+MTX)	MTX+LEF combination	Injectable anti-TNF (ie, etanercept)	Infused anti-TNF (ie, infliximab)
Year of FDA approval	N/A	N/A	1998-2009	1999-2009
How taken	Pills	Pills	Injection at home in fat	Injection at clinic
Frequency	Twice a day (3 pills) + once a week	Once a day (2 pills) + once a week	Every 1-4 weeks	Every 4-8 weeks
Benefits				
Power to suppress arthritis (ACR 20)	57 of 100 will improve	59 of 100 will improve	67 of 100 will improve	60 of 100 will improve
Power to slow joint damage (0-4+)	3+	3+	4+	4+
Harms				
Risk of serious infection (hospitalization/100 patient years of use)	3 in 100	4 in 100	5 in 100	6 in 100
Other risks and side effects	Nausea, fatigue, liver scarring, low blood levels, lung scarring	Nausea, fatigue, liver scarring, low blood levels, lung scarring	Injection site reaction, immune reaction, rare infection (PML)	Infusion reaction, immune reaction, rare infection (PML)
Special population considerations	Avoid pregnancy, hepatitis C; caution in kidney disease; limit alcohol	Avoid pregnancy, hepatitis C; caution in kidney disease; limit alcohol	Avoid pregnancy, TB reactivation, fungus, or virus; worsening heart failure	Caution with pregnancy, TB reactivation, fungus, or virus; worsening heart failure
Practical Issues				
Safety monitoring plan (ACR guidelines)	Pretreatment: CXR, hepatitis B and C; labs every 1-3 months	Pretreatment: CXR, hepatitis B and C; labs every 1-3 months	Pretreatment: CXR, hepatitis B and C, and TB test; labs every 6 months; yearly TB test	Pretreatment: CXR, hepatitis B and C, and TB test; labs every 6 months; yearly TB test
What is my monthly cost? (dependent on health plan)				

DMARD=disease modifying anti-rheumatic drug. ACR=American College of Rheumatology. MTX=methotrexate LEF=leflunomide. SSA=sulfasalazine. HCQ=hydroxychloroquine. PML=progressive multifocal leukoencephalopathy. TB=tuberculosis. CXR=chest x-ray.

Updated: April 24, 2019 © Richard W. Martin, MD, MA. Free use for clinical care is permitted without license.



# FACTS AND NUMBERS BEHIND THIS DECISION AID

## FDA Medication User Guides

- Hydroxychloroquine: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/009768s041lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/009768s041lbl.pdf)
- Etanercept [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/103795s5359lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/103795s5359lbl.pdf)
- Infliximab: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/103772s5301MedG.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103772s5301MedG.pdf)
- Leflunomide: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020905s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020905s020lbl.pdf)
- Methotrexate: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/008085s066lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl.pdf)
- Sulfasalazine: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/007073s124lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/007073s124lbl.pdf)

## Cochrane Database of Systematic Reviews <http://www.cochranelibrary.com/topic/Rheumatology/>

- Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic DMARD for rheumatoid arthritis: A network meta-analysis. *Cochrane Database Syst Rev.* 2016 Aug 29;(8): CD010227. Accessed 8/5/2018: <http://dx.doi.org/10.1002/14651858.CD010227.pub2>.

## Other Publications

- Arava (leflunomide) [package insert]. Bridgewater, NJ: Sanofi-aventis U.S LLC; 2016.
- Bathon J, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med.* 2000;343:1586-1593.
- Caporali R, Caprioli M, Bobbio-Pallavicini F, Montecucco C. DMARDS and infections in rheumatoid arthritis. *Autoimmun Rev.* 2008; 8:139-143.
- Carroll GJ, Thomas R, Phatouros CC, et al. Incidence, prevalence and possible risk factors for pneumonitis in patients with rheumatoid arthritis receiving methotrexate. *J Rheumatol.* 1994;21:51-54.
- Chopra A, Saluja M, Lagu-Joshi V, Sarmukadam S. Leflunomide (Arava™) is a useful DMARD in Indian (Asian) patients: a study of 1-year treatment. *Clin Rheumatol.* 2008; 27:1039-1044.
- Donahue KE, Gartlehner G, Jonas DE, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med.* 2008;148(2):124-134.
- Kalden JR, Schattenkirchner M, Sørensen H, et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study. *Arthritis Rheum.* 2003; 48:1513-1520.
- Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev.* 2010 Apr 14;(4):CD008495.
- Kremer J, Genovese M, Cannon GW, et al. Combination leflunomide and methotrexate (MTX) therapy for patients with active rheumatoid arthritis failing MTX monotherapy: open-label extension of a randomized, double-blind, placebo controlled trial. *J Rheumatol.* 2004;31(8):1521-1531.
- Maddison P, Kiely P, Kirkham B, et al. Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. *Rheumatology (Oxford).* 2005; 44:280-286.
- O'Dell JR, Mikuls TR, Taylor TH, et al; CSP 551 RACAT Investigators. Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med.* 2013;369(4):307-318.
- Rose-John S, Winthrop K, Calabrese L. The role of IL-6 in host defence against infections: immunobiology and clinical implications. *Nat Rev Rheumatol.* 2017;13(7):399-409.
- Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis.* 2018;77(6):905-910.
- Sawada T, Inokuma S, Sato T, et al; Study Committee for Leflunomide-induced Lung Injury, Japan College of Rheumatology. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. *Rheumatology (Oxford).* 2009; 48(9): 1069-1072.
- Sharp JT, Strand V, Leung H, Hurley F, Loew-Friedrich I. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum.* 2000; 43:495-505.
- Singh JA, Saag KG, Bridges SL Jr, et al; American College of Rheumatology. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken).* 2016 ;68(1): 1-25.
- Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. *Lancet.* 1999; 353:259-266.
- Walker AM, Funch D, Dreyer NA, et al. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. *Arthritis Rheum.* 1993;36:329-335.

# OPTION TABLE DECISION AID: FOR A PATIENT WITH RHEUMATOID ARTHRITIS CONSIDERING STARTING THEIR THIRD DMARD

	RECOMMENDED OPTIONS				
Medication options	Infused anti-TNF (ie, infliximab)	T-cell modulator (ie, abatacept)	B-cell depletion (ie, rituximab)	Anti-IL-6 (ie, tocilizumab)	JAK Inhibitor (ie, tofacitinib or baricitinib*)
Year of FDA approval	1999-2009	2005	2006	2008	2012, 2018*
How taken	Infusion	Injection or infusion	Infusion	Injection or infusion	Pill
Frequency	Every 4-8 weeks	Injection weekly or infusion monthly	At weeks 0 and 2, then every 6 months	Injection every 1-2 weeks or infusion monthly	Once daily
Benefits					
Power to suppress arthritis (ACR 20)	60 of 100 will improve	68 of 100 will improve	52 of 100 will improve	59 of 100 will improve	56 of 100 will improve
Power to slow joint damage (0-4+)	4+	4+	4+	4+	4+
Harms					
Risk of serious infection (event/100 patient years of use)	6 in 100	3 in 100	5 in 100	6 in 100	3 in 100
Other risks and side effects	Infusion reaction, immune reaction, skin cancer	Worsening COPD	Infusion reaction, immune reaction, rare infection (PML)	↑ liver test, ↑ lipids, ↓ blood counts, immune reaction	↑ liver test, ↑ lipids, ↓ blood counts, diverticulitis, blood clots*
Special population considerations	Caution with pregnancy; TB reactivation, fungus, or virus infection; worsening heart failure	Avoid pregnancy; avoid in hepatitis B; TB reactivation, fungus, or virus infection	Avoid pregnancy; avoid in hepatitis B; TB reactivation, fungus, or virus infection	Avoid pregnancy; TB reactivation, fungus, or virus infection; diverticulitis; BCP less effective	Avoid pregnancy; TB reactivation, fungus, or virus infection; caution in kidney disease
Practical Issues					
Safety monitoring plan (ACR guidelines)	Pretreatment: CXR, hepatitis B and C, TB test; labs every 6 months; yearly TB test	Pretreatment: CXR, hepatitis B and C, TB test; labs every 6 months; yearly TB test	Pretreatment: CXR, hepatitis B and C, TB test; labs every 6 months; yearly TB test	Pretreatment: CXR, hepatitis B and C, TB test; labs every 1-3 months; yearly TB test	Pretreatment: CXR, hepatitis B and C, TB test; labs every 3 months; yearly TB test
What is my monthly cost? (dependent on health plan)					

DMARD=disease modifying anti-rheumatic drug. ACR=American College of Rheumatology. COPD=chronic obstructive pulmonary disease. PML=progressive multifocal leukoencephalopathy. BCP=birth control pills. TB=tuberculosis. CXR=chest x-ray.

# FACTS AND NUMBERS BEHIND THIS DECISION AID

## FDA Medication User Guides

- Abatacept: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/103772s5281MedG.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103772s5281MedG.pdf)
- Baricitinib: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/207924s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf)
- Infliximab: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/103772s5301MedG.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103772s5301MedG.pdf)
- Rituximab: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/103705s5370mg.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5370mg.pdf)
- Tocilizumab: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/125276s117,125472s032lbl.pdf#page=43](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125276s117,125472s032lbl.pdf#page=43)
- Tofacitinib: <https://www.fda.gov/downloads/Drugs/DrugSafety/UCM330702.pdf>

## Cochrane Database of Systematic Reviews <http://www.cochranelibrary.com/topic/Rheumatology/>

- Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic DMARD for rheumatoid arthritis: A network meta-analysis. *Cochrane Database Syst Rev.* 2016 Aug 29;(8): CD010227. Accessed 8/5/2018: <http://dx.doi.org/10.1002/14651858.CD010227.pub2>.

## Other Publications

- Bathon J, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med.* 2000;343:1586-1593.
- Carroll GJ, Thomas R, Phatouros CC, et al. Incidence, prevalence and possible risk factors for pneumonitis in patients with rheumatoid arthritis receiving methotrexate. *J Rheumatol.* 1994;21:51-54.
- Donahue KE, Gartlehner G, Jonas DE, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med.* 2008;148(2):124-134.
- Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev.* 2010 Apr 14;(4):CD008495.
- Rose-John S, Winthrop K, Calabrese L. The role of IL-6 in host defence against infections: immunobiology and clinical implications. *Nat Rev Rheumatol.* 2017;13(7):399-409.
- Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis.* 2018;77(6):905-910.
- Singh JA, Saag KG, Bridges SL Jr, et al; American College of Rheumatology. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken).* 2016 ;68(1):1-25.